REMARKS

Claims 1-16, and 18-74 are pending and under examination with claims 66-69 having been withdrawn from consideration as being directed to a non-elected invention. Applicants reserve the right to pursue these claims in a later filed application claiming the benefit of the subject application. By the present communication, no claims have been added or canceled, and Claims 34 and 71 have been amended. Support for the amendments can be found in the specification and the claims as originally filed. In particular, support for the amendments can be found, for example, in paragraphs [0042] to [0043]. Accordingly, these amendments do not raise an issue of new matter, and entry thereof is respectfully requested.

Rejection Under 35 U.S.C. § 101

Applicants respectfully traverse the rejection of claims 34-65 and 70-74 under 35 U.S.C. § 101 as allegedly being directed to non-statutory subject matter. Applicants respectfully submit that the claims are directed to statutory subject matter. Nevertheless, without acquiescing to the reasoning of the Action, and in order to further prosecution of the instant application, independent claims 34 and 71 have been amended to recite "determining on a computer at least one flux distribution." Applicants respectfully submit that, as amended, the claims specifically recite determining on a computer at least one flux distribution and therefore tie the claimed methods to a specific machine. Accordingly, Applicants respectfully submit that the claimed methods are directed to statutory subject matter and request that this rejection be withdrawn.

Rejections Under 35 U.S.C. § 103

Applicants respectfully traverse the rejection of claims 34-42, 44, 45, 48, 49, 51-63 and 70-74 under 35 U.S.C. § 103 as allegedly obvious over Hatzimanikatis et al. (*AICHE Journal* 42(5): 1996-2005 (1996); hereinafter "Hatzimanikatis"), in view of Varma et al. (*Bio/Technology* 12:994-998 (1994); hereinafter "Varma"). Applicants respectfully maintain, for the reasons of record, that Hatzimanikatis et al. does not teach or suggest Applicants' claimed methods.

As discussed in the previous response, Hatzimanikatis states in the abstract that "[A] regulatory superstructure proposed contains all alternative regulatory structures that can be considered for a given pathway" (emphasis added). As discussed previously, Hatzimanikatis, at most, describes a mathematical framework for determining changes in regulatory structure and strength that should be considered to optimize a particular metabolic process (see page 1278, 2nd col., 3rd paragraph). Hatzimanikatis indicates that it deals with a mathematical description of a metabolic pathway with a postulated number of regulatory loops and that the objective is to determine which of the regulatory loops should be retained (page 1279, 1st col., 1st complete paragraph). Hatzimanikatis further describes consideration of a "regulatory superstructure" in which "every metabolite in the system can potentially regulate any enzyme in that system" (page 1279, 1st col., 3rd complete paragraph; emphasis added). Such a "regulatory superstructure" is clearly a postulation of possible regulatory loops since "every metabolite" cannot regulate "any enzyme." Hatzimanikatis concludes at page 1289, left column, final paragraph:

> The problem of designing the regulatory structures built around a given metabolic reaction network was formulated as a MILP optimization problem. A synthesis approach has been proposed which assumes that the metabolic pathway of interest has no regulation, and considers which regulatory structure optimizes the objective. [emphasis added]

Thus, it is clear that Hatzimanikatis describes designing regulatory structures. However, Hatzimanikatis provides no teaching or suggestion of the claimed methods, in which a constraint set is provided for the plurality of reactions related in a data structure to a plurality of reactions of a biochemical reaction network and where the constraint set comprises a variable constraint for the regulated reaction.

Applicants note the acknowledgement on page 8 of the Office Action of the lack of disclosure in Hatzimanikatis, where it is acknowledged that "Hatzimanikatis et al. does not teach a data structure or database comprising reactions wherein the reactants and products are identified and are related or linked to a stoichiometric coefficient." Therefore, based on the

acknowledgement in the Office Action of the lack of disclosure in Hatzimanikatis, the alleged *prima facie* case of obviousness must rely on the disclosure in the newly cited reference of Varma. In this regard, the Office Action discusses Varma in three places. On page 8 of the Office Action, Varma is discussed, indicating that "[T]he article of Varma et al. studies metabolic flux balancing. Specifically, equation 1 on page 994 and Figure 1 on 995 of Varma et al. teach use of stoichiometric matrices to relate reactants to products in metabolic processes." On page 13 of the Office Action, Varma is discussed in the context of claim 61. "The last full paragraph of column 2 on page 994 of Varma et al. describes that the mass balancing techniques are equally applicable to degradation as well as formation of metabolites." In the final discussion of Varma, in the paragraph bridging pages 14-15 of the Office Action, it is asserted that "[I]t would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the flux distribution and reaction optimization of Hatzimanikatis et al. by use of the stoichiometric analyses of Varma et al. wherein the motivation would have been that the stoichiometric matrices of Varma et al. are necessary to provide an accurate mass balance over the metabolic system [see last full paragraph of column 2 on page 994 of Varma et al.]."

Varma, at best, appears to be a review article discussing metabolic flux balancing. However, Applicants respectfully submit that, contrary to the assertion in the Office Action on page 14, one skilled in the art would have had no motivation to combine the teachings of Hatzimanikatis describing designing a regulatory structure from a number of possible regulatory structures with those of Varma, and certainly no motivation based on the passage and characterization of Varma articulated in the Office Action as allegedly providing such motivation. Starting on page 994, 2nd column of Varma, the reference discusses their mathematical structure.

> As shown in Figure 1, the catabolic pathways serve to degrade the carbon source into precursors from which monomers are synthesized which are then polymerized and assembled into cellular components. Material balances can be written around a system comprised of a network of metabolic reactions. Inputs to the system include the carbon source provided in the culture medium while the

> outputs include by-products, additional biomass generated, as well as any maintenance requirements. The dynamic material balance determines metabolite concentrations, provided that the kinetics of the enzymatic reactions are known. The flux balance model eliminates this requirement by treating the metabolic reaction fluxes as the unknown quantities that need to be determined.
>
> A metabolic quasi-steady state is assumed. This assumption is based on the fact that metabolic transients are typically rapid compared to cellular growth rates and environmental changes. The consequence of this assumption is that all metabolic fluxes leading to the formation and degradation of any metabolite must balance, leading to the flux balance equation:
>
> $$S \cdot v = b \qquad (1)$$
>
> where S is a matrix containing the stoichiometry of the catabolic reactions, v is a vector of the 'n' metabolic reaction rates, and b is a vector containing the net metabolite uptake by the cell. Equation (1) is typically underdetermined since the number of fluxes normally exceeds the number of metabolites.
>
> Therefore, a plurality of solutions exists and the cell is faced with an infinite number of choices on how it can distribute its metabolic fluxes. The choices are constrained by the stoichiometric matrix and these constraints form a domain of stoichiometrically allowable behavior as illustrated in Figure 2. This domain may be thought of as defining the "metabolic genotype" of the strain since it describes the metabolic flux distributions that can be achieved with the metabolic enzymes that the strain possess. The enzyme "portfolio" of a strain thus determines its "metabolic genotype". It can be changed through genetic engineering. [citations omitted]

The above passage includes the last full paragraph of column 2 on page 994 of Varma, asserted in the Office Action to provide the alleged motivation to modify Hatzimanikatis, as well as the preceding and following paragraphs. However, Applicants can discern no teaching or suggestion in the cited passage "that the stoichiometric matrices of Varma are necessary to provide an accurate mass balance over the metabolic system," as asserted in the Office Action, nor any teaching or suggestion that would have motivated one skilled in the art to modify the teachings of Hatzimanikatis or combine the teachings of this reference with Varma. Therefore, Applicants respectfully disagree with the characterization of Varma asserted in the Office Action and respectfully submit that, in the absence of the alleged teaching in Varma, a *prima facie* case of obviousness has not been established.

The U.S. Patent and Trademark Office recently promulgated guidelines for Examiners in making obviousness determinations in view of the U.S. Supreme Court's decision in *KSR Int'l Co. v. Teleflex Inc.* Examination Guidelines for Determining Obviousness under 35 U.S.C. 103 in View of the Supreme Court Decision in KSR International Co. v. Teleflex Inc., 72 Fed. Reg. 57,526 (2007) ("Guidelines") One important feature of the Guidelines is an *explicit requirement* that an Examiner provide articulated reasons for the factual determinations underlying an asserted *prima facie* case of obviousness. This focus is consistent with the rule set down in the *KSR* decision that a factfinder must provide "reasons" why an invention would have been obvious to one of ordinary skill in the art." *KSR* at 1741. In explicating this aspect of the Supreme Court's decision, the Guidelines set forth several different rationales that can be used to support an obviousness rejection. The Guidelines further set forth explicit factual findings that an Examiner must articulate to support an obviousness rejection under each rationale. In the present case the Examiner has applied the "teaching, suggestion or motivation" test, identified in the guidelines as rationale (G). For an obviousness rejection based on this rationale for combining references, the Examiner *is required to articulate* the following: (1) a finding that there was some teaching, suggestion, or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine reference teachings; (2) a finding that there was reasonable expectation of success; and (3) whatever additional findings based on the Graham factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness. While it is proper for the motivation to combine to be implicit and be found in the knowledge of one of ordinary skill in the art, or, in some cases, the nature of the problem to be solved, the Examiner has not articulated where such motivation is found other than the asserted teachings of Varma which, as discussed above, are not found in the cited passage of Varma. *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398; 127 S. Ct. 1727; 167 L. Ed. 2d 705, 82 USPQ2d 1385, 1395 (2007).

Furthermore, the present Office Action fails to articulate a finding that there would have been a reasonable expectation of success when combining the cited references. Even if,

arguendo, one were to have combined the teachings of Hatzimanikatis with those of Varma, one skilled in the art would have had no reasonable expectation of success of arriving at the claimed methods, in which a constraint set is provided for the plurality of reactions in the data structure, where the constraint set comprises a variable constraint for the regulated reaction, and determining at least on flux distribution that minimizes or maximizes an objective function when the constraint set is applied to the data structure. No such teaching or suggestion can be found in either of Hatzimanikatis or Varma, when considered alone or in combination, and therefore Applicants respectfully submit that a *prima facie* case of obviousness has not been established.

Applicants respectfully submit, as discussed above, that neither of Hatzimanikatis nor Varma, alone or in combination, teaches or suggests the claimed methods and that a *prima facie* case of obviousness has not been established. Accordingly, Applicants respectfully maintain that the claimed methods are unobvious over Hatzimanikatis, alone or in combination with Varma, and withdrawal of the rejection is respectfully requested.

Applicants respectfully traverse the rejection of claims 1-12, 14, 15, 18-28, 30, 32, 33, 43 and 46 under 35 U.S.C. §103(a) as allegedly being obvious over Hatzimanikatis, *supra*, in view of Varma, *supra*, and further in view of Grewal, *et al.* (*Protein Engineering* 7:205-211(1994); hereinafter, "Grewal"). This rejection relies on Hatzimanikatis in view of Varma, and Applicants have set forth above the deficiencies of Hatzimanikatis in view of Varma. Furthermore, Applicants discussed in the previous response that Grewal does not cure the deficiencies of Hatzimanikatis, nor does Grewal cure the deficiencies of Hatzimanikatis in view of Varma. Accordingly, the claimed computer readable medium or media and methods are unobvious over Hatzimanikatis in view of Varma and/or Grewal, and withdrawal of the rejection is respectfully requested.

Applicants respectfully traverse the rejection of claims 64 and 65 under 35 U.S.C. §103(a) as allegedly being obvious over Hatzimanikatis, *supra*, in view of Varma, *supra*, and further in view of Liao, *et al.* (Biotechnology and Bioengineering 52:129-140 (1996);

hereinafter, "Liao"). This rejection relies on Hatzimanikatis in view of Varma and, as discussed above, Applicants have set forth the deficiencies of Hatzimanikatis in view of Varma. Furthermore, Applicants discussed in the previous response that Liao et al. does not cure the deficiencies of Hatzimanikatis, nor does Liao cure the deficiencies of Hatzimanikatis in view of Varma. Accordingly, the claimed methods are unobvious over Hatzimanikatis in view of Varma and/or Liao, and withdrawal of the rejection is respectfully requested.

Applicants respectfully traverse the rejection of claims 31 under 35 U.S.C. §103(a) as allegedly being obvious over Hatzimanikatis, *supra*, in view of Varma, *supra*, and Grewal, *supra,* and further in view of Liao, *supra*. As discussed above, Applicants have set forth the deficiencies of Hatzimanikatis in view of Varma Further, the deficiencies of Grewal and Liao are also discussed above, neither of which can cure the deficiencies of Hatzimanikatis in view of Varma. Accordingly, the claimed computer readable medium or media are unobvious over Hatzimanikatis in view of Varma and/or Grewal and/or Liao, and withdrawal of the rejection is respectfully requested.

Applicants respectfully traverse the rejection of claim 50 under 35 U.S.C. § 103 as allegedly obvious over Hatzimanikatis, *supra*, in view of Varma, *supra*, and further in view of Kim *et al*., U.S. publication 2002/00087275 (hereinafter "Kim"). This rejection relies on Hatzimanikatis in view of Varma, and Applicants have set forth above the deficiencies of Hatzimanikatis in view of Varma. Furthermore, Applicants discussed in the previous response that Kim does not cure the deficiencies of Hatzimanikatis, nor does Kim cure the deficiencies of Hatzimanikatis in view of Varma. Accordingly, the claimed method is unobvious over Hatzimanikatis in view of Varma and/or Kim, and removal of the withdrawal is respectfully requested.

Applicants respectfully traverse the rejection of claim 16 under 35 U.S.C. § 103 as allegedly obvious over Hatzimanikatis, *supra*, in view of Varma, *supra*, and Grewal, *supra*, and further in view of Kim, *supra*. As discussed above, Applicants have set forth the deficiencies of Hatzimanikatis in view of Varma. Further, the deficiencies of Grewal and Kim are also

discussed above, neither of which can cure the deficiencies of Hatzimanikatis in view of Varma. Accordingly, the claimed computer readable medium or media are unobvious over Hatzimanikatis in view of Varma and/or Grewal and/or Kim, and withdrawal of the rejection is respectfully requested.

Applicants respectfully traverse the rejection of claims 13 and 47 under 35 U.S.C. § 103 as allegedly obvious over Hatzimanikatis, *supra*, in view of Varma, *supra*, and Grewal, *supra*, and further in view of Vissing, (*Neurology* 47:766-771 (1996); hereinafter "Vissing"). This rejection relies on Hatzimanikatis in view of Varma, and Applicants have set forth above the deficiencies of Hatzimanikatis in view of Varma. Furthermore, as discussed in the previous response, Vissing does not cure the deficiencies of Hatzimanikatis, nor does Vissing cure the deficiencies of Hatzimanikatis in view of Varma. Accordingly, the claimed computer readable medium or media and method are unobvious over Hatzimanikatis in view of Varma and/or Vissing, and withdrawal of the rejection is respectfully requested.

Applicants respectfully traverse the rejection of claim 29 under 35 U.S.C. § 103 as allegedly obvious over Hatzimanikatis, *supra*, in view of Varma, *supra*, and Grewal, *supra*, and further in view of Callis (*Plant Cell* 7:845-857 (1995); hereinafter "Callis"). As discussed above, Applicants have set forth the deficiencies of Hatzimanikatis in view of Varma and/or Grewal. Moreover, Applicants respectfully submit that Callis does not cure the deficiencies of Hatzimanikatis in view of Varma and/or Grewal. At best, Callis is a review article discussing regulation of protein degradation in plants. Furthermore, Applicants respectfully submit that the passage on page 850 of Callis referred to in the Office Action describes the senescent process in unpollinated pea ovaries and the induction of a cysteine protease during this process. Although the reference discusses expression and characteristics of the open reading frame of the encoded cDNA, there is no teaching or suggestion of annotation of at least one reactant in a plurality of reactants or at least one reaction in a plurality of reactions by assignment to an open reading frame, as in Applicants' claim. Applicants further respectfully disagree with the assertion in the Office Action that one skilled in the art would have been motivated to assign open reading frames to specific proteins "where the motivation would have been that such an assignment

facilitates mapping between DNA and proteins," referring to the passage of Callis discussed above. Applicants respectfully submit that, other than discussing the senescent process of unpollinated pea ovaries, Callis provides no such motivation as asserted in the Office Action. Therefore, Applicants respectfully submit that Callis does not cure the deficiencies of Hatzimanikatis in view of Varma and/or Grewal. Accordingly, the claimed computer readable medium or media is unobvious over Hatzimanikatis in view of Varma and/or Grewal and/or Callis, and removal of the rejection is respectfully requested.

In light of the amendments and remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect.

CONCLUSION

In summary, for the reasons set forth herein, Applicants submit that the claims are in condition for allowance and respectfully request a notice to this effect. If the Examiner would like to discuss any of the issues raised in the Office Action, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

The Commissioner is hereby authorized to charge $555.00 as payment for the Petition for the Three-Month Extension of Time fee to Deposit Account No. 07-1896. Additionally, the Commissioner is hereby authorized to charge any other fees that may be due in connection with the filing of this paper, or credit any overpayment to Deposit Account No. 07-1896.

Respectfully submitted,

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